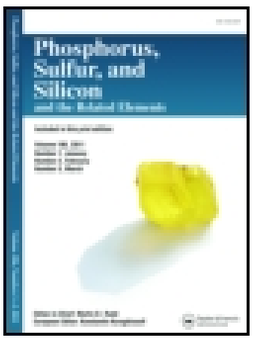

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SHORT COMMUNICATION

Rational synthesis of α-hydroxyphosphonic derivatives including dronic acids

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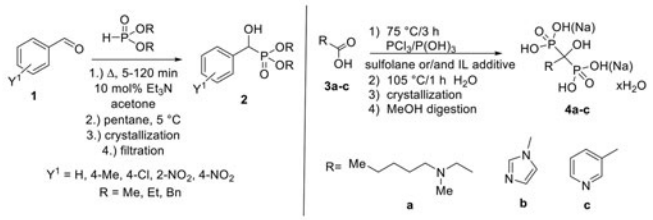
ABSTRACT

New, green methods have been elaborated for the syntheses of α-hydroxyphosphonates and α-hydroxymethylenebisphosphonic derivatives (HMBPs, dronates). α-Hydroxyphosphonates were prepared via the Pudovik reaction, while the synthesis of HMBPs has been performed in the three-component reaction of carboxylic acids, phosphorus trichloride and phosphorus acid.

GRAPHICAL ABSTRACT



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α-Hydroxymethylenebisphosphonates; α-hydroxyphosphonates; Pudovik reaction; green syntheses; sulfolane; ionic liquid

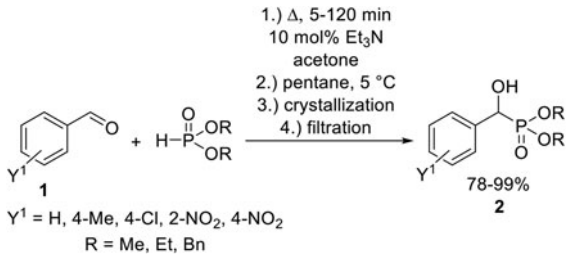
Introduction

α-Hydroxyphosphonic acids and related derivatives are of special importance due to their biological activity.[1] α-Hydroxymethylenebisphosphonic derivatives represent a significant class within this family, as they are commercially available drugs against osteoporosis.[2] Nowadays, environmentally-friendly-friendly methods including suitable reagents and solvents are in the focus. The application of ionic liquids (ILs) as solvents or additive is a new trend.[3] During our research targeting the synthesis of α-hydroxyphosphonates and α-hydroxymethylenebisphosphonic derivatives, special efforts were devoted to green chemical aspects.

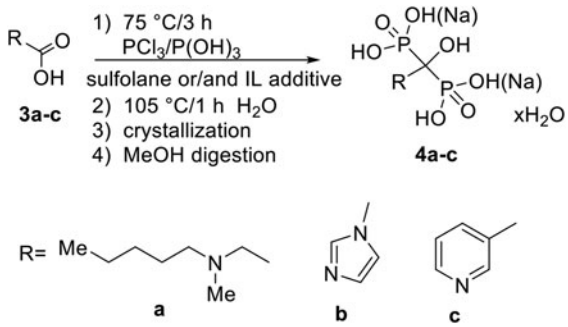
Results and discussion

α-Hydroxyphosphonates are usually synthesized in the Pudovik reaction of an oxo compound and dialkyl phosphite, under catalytic and solvent-free conditions. However, in most of the cases, a considerable amount of organic solvents is used during the work-up including extraction, column chromatography or recrystallization.[4,5]

A new, solvent-economic variation of the Pudovik reaction was elaborated by us.[6] According to our new method, for the triethylamine-catalyzed reaction of a substituted benzaldehyde (**1**) and dialkyl phosphite, a minimal amount of acetone was used. After the reaction was complete, some *n*-pentane precipitant was added to the mixture, resulting in the crystallization of product **2** that could be separated by a simple filtration (Scheme 1).[6,7] Although, a small quantity of acetone and pentane was used in the reaction, there was



Scheme 1. Solvent-economic synthesis of α-hydroxyphosphonates *via* the Pudovik reaction.



Scheme 2. Synthesis of dronic acid derivatives in sulfolane, or in the presence of an IL additive, or using both agents.

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Table 1. Yields and purities of dronic acid derivatives in sulfolane, or in the presence of an IL additive, or using both agents.

		P-reagents (equiv.)			
Dronic derivatives	Solvent or additive	PCl_3	H_3PO_3	Purity (%)	Yield (%)
Ibandronate (**4a**)	Sulfolane	3	2	100	83
	0.1 equiv. [bmim][BF_4]	3	2	99	90
Zoledronic acid (**5a**)	Sulfolane	2	2	100	74
	0.6 equiv. [bmim][BF_4]	2	2	99	75
	Sulfolane + 0.6 equiv. [bmim][BF_4]	2	2	99	93
Risedronic acid (**6a**)	Sulfolane	2	2	100	58
	0.6 equiv. [bmim][BF_4]	2	2	100	66

no need for more solvent, as no purification steps were necessary.

The most often applied P-reagents in the synthesis of α-hydroxymethylenebisphosphonic derivatives are phosphorus trichloride and phosphorous acid, and the preferred solvent is methanesulfonic acid (MSA). But MSA is not considered an environmentally friendly solvent. The synthesis of a few dronic acid derivatives was also performed in sulfolane, or in the presence of an IL additive, or in the combination of sulfolane/IL.[8] This approach was extended to the synthesis of ibandronate (**4a**)[9] and two representatives of the third generation agents zoledronic acid (**4b**)[10] and risedronic acid (**4c**)[11] (Scheme 2, Table 1). The joint use of the IL additive and sulfolane as the solvent was synergetic affording highly valuable zoledronic acid in a record yield of 93%.[11]

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